LETTERS TO THE EDITOR

Topical Retinoids: Another Piece for the Retinoid-Cigarette-Lung Cancer Puzzle?

To the Editor:

The possibility of a role for topical retinoids might add an additional piece to the retinoid-cigarette-lung cancer puzzle.1

A poster2 at the 2005 annual meeting of The Society for Investigative Dermatology described the halting of a topical retinoid study because of an excess of deaths from lung cancer and pulmonary disease in the treated group. A 10-center, 1131-participant trial had been sponsored by the Department of Veterans Affairs to study the ability of 0.1% tretinoin cream to reduce the development of keratinocyte carcinoma. Participants (average age, 71 years) applied tretinoin cream or placebo to their face and ears every day for 6 years. The study was stopped 6 months before completion because of deaths from pulmonary disease (12 versus two) and non-small cell lung cancer (11 versus 4) but not other cancers (20 versus 18) or cardiac disease (19 versus 16) in the tretinoin cream versus placebo groups.

Presenters of the poster suggested that failure to randomize for factors such as smoking had flawed the study design. With further analysis, they found differences in Charlson comorbidity index, age, and smoking. Each of those differences favored worse prognosis in the tretinoin group, but all differences were small and statistically insignificant. Cox multivariate regression with those variables and treatment group revealed that, with joint consideration of all of those variables, the mortality difference between the groups was not statistically significant.

The authors concluded that tretinoin did not cause the mortality difference between the groups and that, in retrospect, the termination of the intervention was unnecessary. They did not consider the possibility that absorbed tretinoin might have acted like dietary carotinoid in cigarette smokers.

A possible mechanism for such an effect was described in 2004 by Harder et al.3 from Kiel and Stockholm. They added tretinoin to foreskin keratinocytes in cell culture and looked for an effect on the synthesis of beta-defensins. There was a profound reduction in defensins-1, -2, -3, and -4. Their conclusion was that retinoic acid “might downregulate the innate chemical defense system of human skin.”

Like the skin, the bronchial epithelium confronts the environment and, like the skin, uses defensins as part of its innate immune response capability.4 Bronchial defensins are increased in squamous metaplasia and in lung cancer.

By reducing the defensin effect, absorbed topical retinoid could be responsible for an increase in the appearance of lung cancer without the need to postulate a carcinogenic mechanism. The same explanation would account for the excess of deaths from non-malignant pulmonary disease in the halted VA trial.

Whether enough tretinoin is absorbed from topical application to affect the bronchial production of defensins or other agents of innate immunity needs to be investigated. The Novena (OrthoNeutrogena, Raritan, NJ) package insert describes the systemic absorption of tretinoin as ranging from 1% to 31% from pretreatment levels even after chronic use.5

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REFERENCES

Temozolomide as Prophylaxis for Brain Metastasis in Non-small Cell Lung Cancer

To the Editor:

We read with interest the article by Choong et al.1 regarding the use of temozolomide and irinotecan in non-small cell lung cancer (NSCLC) with particular attention to the development of brain metastasis. They suggested that temozolomide had “little role in the prophylaxis against metastasis in NSCLC” based on their results. They observed only three of 37 patients developing brain metastasis in this phase II study. (Nine patients entered the study with a history of radiation-treated brain metastasis; the patients had no clinical evidence of central nervous system (CNS) progression while on study.) As 50% of patients with NSCLC would be expected to develop brain metastasis (with median time to development of 6–9 months), we came to a different conclusion. In this regard, in a prospective trial of well-staged (including head magnetic resonance imaging) stage IIIA and IIIB NSCLC that we reported,2 20 of 25 patients treated with combined modality therapy relapsed within less than 12 months, and of these, eight patients (40% of all relapsing patients, 32% of

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732 Journal of Thoracic Oncology • Volume 1, Number 7, September 2006
all patients) failed initially in the CNS. Four additional patients subsequently developed CNS metastases, for an overall CNS failure rate of 12 of 20 (relapsing) patients, or 60%, representing almost 50% of all well-staged stage IIIA and B NSCLC patients failing in the CNS. (These failures were detected clinically because routine post-study magnetic resonance imaging was not performed). Thus, we hypothesize that the low incidence of 8% CNS metastasis in the Choong et al. study might in fact suggest that temozolomide could potentially have controlled microscopic CNS disease in a proportion of patients.

Consistent with this supposition, an earlier study reported by Adonizio et al. using temozolomide as a single agent produced similar results: five of 38 patients entered the study with treated brain metastasis; two had CNS progression and only one patient developed brain metastasis on study for an incidence of 3%.

These results, taken collectively, provide putative support for a well-structured prospective clinical trial to test the value of temozolomide for “prophylaxis” (i.e., in reality, the treatment of micrometastatic disease) of the CNS. We agree that the role of temozolomide as prophylaxis against central nervous system metastasis should be tested us to reply.

To the Editor:

On behalf of the coauthors, we are replying to the letter by Dr. Robins and colleagues.

In our study evaluating temozolomide and irinotecan as second-line agents, we determined that the response rate was only 9% with a short median time to progression of 1.8 months. As a result, the duration of treatment was short (median two cycles or 6 weeks). In this brief period, 67% of our subjects had progressive disease including three patients who developed new symptomatic brain metastasis. Because brain imaging was not required post-study, the incidence of asymptomatic brain metastasis is unknown but probably higher than 8%. In addition, our trial was not designed to specifically address the effect of temozolomide on brain metastasis. We agree that the role of temozolomide as prophylaxis against central nervous system metastasis should be evaluated in a large, well-designed prospective trial.

Thank you very much for allowing us to reply.

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